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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	10

DATE MAILED: 11/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/398,522	ISSA, JEAN-PIERRE	
	Examiner	Art Unit	
	Jeanine A Enewold Goldberg	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *27 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 25-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .

19) ☐ Notice of Informal Patent Application (PTO-152)

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DETAILED ACTION

Specification

1. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

For example purposes, the specification provides hyperlinks on page 67, line 20 and pages 68, lines 7 and 10.

Election/Restrictions

2. Applicant's election of Group III in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 10-13, 19, 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a cellular proliferative disorder in a subject by contacting a nucleic acid containing specimen with an agent that provides a determination of the methylation state of CACNA1G or other

genes whose methylation status is known to be associated with a cellular proliferative disorder and detecting methylation status of the gene to detect a tumor, does not reasonably provide enablement for a method for detecting a cellular proliferative disorder in a subject by contacting a nucleic acid containing specimen from the subject with an agent that provides a determination of the methylation state of APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 or or other genes whose methylation status was not previously known to be associated with a cellular proliferative disorder such that a cellular proliferative disorder may be detected. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method for detecting **any** cellular proliferative disorder in a subject by contacting a nucleic acid containing specimen from the subject with an agent that provides a determination of the methylation state of **any** gene such that a cellular proliferative disorder may be detected.

The specification teaches that aberrant methylation of CGIs have been detected in genetic disease such as the fragile-X syndrome, in aging cells and in neoplasia (pg. 3, lines 21-23). The specification teaches the CpG-rich regions from APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 which are hypermethylated (pg. 7, lines 10-11, Figures 4A-4F). The specification teaches that methylation analysis of CACNA1G was performed (pg. 24). The

specification explicitly teaches that whether large CpG islands are aberrantly methylated in cancer is not apparent (pg. 24).

The art teaches that tissues are both hyper and hypo methylated as indicative of cancerous tissue. Balyin et al. (herein referred to as Balyin-1) teaches alterations in DNA methylation as a fundamental aspect of neoplasia (Advances in Cancer Research, Vol. 72, pg. 141-196, 1998). Baylin-1 discusses not only hypermethylation as associated with cancer, but additionally teaches that hypomethylation is associated with cancer. In the discussion, Baylin-1 teaches that in a number of models of carcinogenesis decrease in numbers of methyl groups appear to begin early in tumor progression and before the appearance of frank tumor formation (pg. 151). Baylin teaches that there is a clear association of DNA hypomethylation with tumors, however, the exact ramifications of this change for steps in tumor progression are poorly understood (pg. 151). Hypomethylation patters have been described for oncogenes in tumors. Baylin also teaches hypermethylation in cancer (pg. 152). Baylin provides several examples of CpG island hypermethylation associated with transcriptional inactivation of specific genes in neoplastic cells including Rb, VHL, p16, p15, E-cadherin, hMLH1, and ER (Table 2). Further, Nelson et al. (herein referred to as Nelson) teaches a method for detecting proliferative disorder associated with glutathione-S-transferase (GSTP1) which detect hypermethylation of GSTP1 promoter in a tissue sample (abstract). As seen in Figure 5, hypermethylation does not appear to occur in normal tissues. Nelson teaches that a hypermethylated promoter for the human GSTP1 positively correlates with prostatic carcinogenesis (col. 3, lines 5-10). In

a distinct article, Baylin et al. (herein referred to as Baylin-2) teaches that HIC-1 is within a CpG island which is abnormally methylated in many different types of tumors. Baylin-1 teaches hypermethylation of HIC-1 was analyzed in primary tumors and cultured cells lines (col. 22, lines 36-40).

It is well known in the art that hypo and hyper methylation appear to be associated with neoplasia, however, the art provides no guidance as to whether any specific gene elicits a hyper or hypo methylation state in any genes (broad Claim 10). The specification only shows CACNA1G with experimental data which provides guidance to the skilled artisan of hypermethylation. The specification teaches APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4, are hypermethylated (pg. 7). The specification has not provided any correlation between tumor and normal tissue regarding hypermethylation for APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 such that the skilled artisan would be able to take the information and detect cellular proliferative disorders. It would be unpredictable that these specific genes are infact differentially methylated in cancerous tissue and normal tissue. And it would require undue experimentation for the skilled artisan to perform the necessary experimentation to determine whether the listed genes are only hypermethylated in specific tumors and other cellular proliferative disorders. The skilled artisan would be required to sample tumor and normal cells from a clinical study to ascertain whether the tumors are hypermethylated and then determine whether this is only observed in tumors. Genes are known to be methylated at certain stages, however, mere methylation is not

necessarily indicative of cancer. Absent showing that these genes are in fact differentially methylated in tumors and normal tissue, the skilled artisan would be unable to practice the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 10-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 10-24 are indefinite over the recitation "cellular proliferative" in claim 10, lines 8, because it is unclear what a cellular proliferative is. Additionally, the claim has not provided for a cellular proliferative such that the recitation lacks proper antecedent basis. It is presumed that disorder has inadvertently been omitted from the claim such that it should read "cellular proliferative disorder".

B) Claim 21 is unclear because it is unclear whether the pairs are specific pairs such that 1 and 2 are a pair and 3 and 4 are a pair or whether consecutive pairs may include primers of 2 and 3 and 3 and 4.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 10-11, 13, 19, 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Nelson et al (US Pat. 5,552,277, September 1996).

Nelson et al. (herein referred to as Nelson) teaches a method of detecting a cellular proliferative disorder which included contacting a nucleic acid with an agent to determine the methylation state of at least one gene associated with the regulatory region of the gene and identifying aberrant methylation wherein aberrant methylation is indicative of a cellular proliferative disorder. Specifically, Nelson teaches a method for detecting proliferative disorder associated with glutathione-S-transferase (GSTP1) which detect hypermethylation of GSTP1 promoter in a tissue sample (abstract). As seen in Figure 5, hypermethylation does not appear to occur in normal tissues. Nelson teaches that a hypermethylated promoter for the human GSTP1 positively correlates with prostatic carcinogenesis (col. 3, lines 5-10)(limitations of Claims 10, 13, 24). Nelson teaches using a "reagent" which is a probe or PCR primer (col. 3, lines 25-30)(limitations of Claim 19). Nelson teaches that any specimen may be used, and a preferred sample is tissue of urogenital origin specifically tissue of the prostate (col. 3, lines 52-60)(limitations of Claim 22). Moreover, the specimen may be urine or blood (col. 3, lines 60-65)(limitations of Claims 23). Nelson teaches that 400 nucleotides lying

immediately 5' of the transcriptional site contain nearly 72% CG nucleotides with 41 CpG dinucleotides (col. 11, lines 55-60)(limitations of Claim 11). Nelson teaches that there "was no evidence of GSTP1 promoter hypermethylation in any of the normal prostatic tissues" (col. 13, lines 24-25).

6. Claims 10-11, 13, 19, 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Baylin et al (US Pat. 5,756,668, May 1998).

Baylin et al. (herein referred to as Baylin) teaches a method of detecting a cellular proliferative disorder which included contacting a nucleic acid with an agent to determine the methylation state of at least one gene associated with the regulatory region of the gene and identifying aberrant methylation wherein aberrant methylation is indicative of a cellular proliferative disorder. Specifically, Baylin teaches that HIC-1 is within a CpG island which is abnormally methylated in many different types of tumors (limitations of Claim 10 and 11). PCR can be used to detect the methylation status of the HIC-1 gene using oligonucleotide primers (col. 12, lines 40-45)(limitations of Claim 19). Baylin teaches hypermethylation of HIC-1 was analyzed in primary tumors and cultured cells lines (col. 22, lines 36-40)(limitations of Claim 13). Baylin teaches that preferred samples include urogenital, prostate thymus, lung, testis and ovarian tissue (col. 12, lines 55-60)(limitations of Claim 22-23). Baylin teaches various disorders are detectable by the method including astrocytoma, colon cancer, lung cancer, prostate cancer (col. 12, lines 60-65)(limitations of Claims 24).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 10-11, 13, 22-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,552,227. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn broadly such that the instant claims encompass the claims of 5,552,227.

Conclusion

8. No claims allowable over the art.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Toyota et al (Genbank AF124351, June 2, 1999) teaches a nucleic acid molecule which is 100% identical to the claimed CACNA1G nucleic acid. It is noted that

the inventorship is not identical to the instant application and was publicly available prior to the filing of the application.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
October 25, 2000

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800